Exhibit 38

focus on surgeon professionalism. Poor ABSITE performance and minority status were associated with frequent bullying. Women were more frequently bullied, and training in a program with more women or with departmental leaders who were women was not associated with decreased bullying. The wide variability in program-level bullying rates suggests that surgical training can occur without bullying.

Limitations include self-reporting of responses, lack of validation of the S-NAQ in educational health care settings (although the expanded questionnaire has been used in surgery previously[2]), and unqueried surgery-specific behaviors (such as forbidding speech in the operating room).

Bullying was a frequent experience reported in surgical training, and it was associated with burnout, thoughts of attrition, and suicidality. Training programs should focus on recognizing and addressing resident bullying to improve the surgical educational experience.[6]

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COMMENT & RESPONSE

Genital Powder Use and Ovarian Cancer

To the Editor Dr O'Brien and colleagues[1] combined data on powder use in the genital area and ovarian cancer from 4 cohort studies and reported an overall hazard ratio (HR) of 1.08 (95% CI, 0.99-1.17). Except for data from the Nurses' Health Study II and additional follow-up, little new information was presented. Previously, combined data from 3 of the cohorts showed an odds ratio (OR) for perineal powder use and ovarian cancer of 1.06 (95% CI, 0.90-1.25).[2] In the latter study, the cohort data did not outweigh the evidence from 24 case-control studies, with a combined OR of 1.31 (95% CI, 1.24-1.39).

A major weakness is that the cohort studies differed in the questions defining whether a woman was exposed to powder. For example, in the Sister Study, the exposure frequency was 14% when exposure in the past year was considered[3] and 27% when exposure at age 10 to 13 years was counted.[1]

None of the cohorts had information on whether talc or cornstarch was used, and none had data on both frequency and duration of use needed for a true dose-response evaluation. Questions about powder use were asked only once, excluding ability to track patterns of use with events such as hormone use or tubal ligation. Without such information, the assumption is that cohort members remained exposed for the entire follow-up ending in 2016. For the Nurses' Health Study, powder exposure had been assessed 34 years prior, in 1982. Is assuming continued exposure for these nurses more reasonable than assuming case-control studies are flawed because cases preferentially recalled talc use well before any major publicity about the association? If recall bias existed, why was the association stronger for particular histologic types of ovarian cancer and no association seen with cornstarch use in 1 case-control study?[4] How would either a case or a control participant forget daily use of talc for decades, the time period of exposure in which the risk lies?[4]

Most women in these cohorts were postmenopausal at assessment of exposure. However, case-control data reveal that the association between talc use and ovarian cancer is stronger for premenopausal women or postmenopausal women who also used hormone replacement.[4] This finding suggests estrogen is involved in the pathway(s) through which talc may cause ovarian cancer—a hypothesis

supported by data showing that coexposure of macrophages to talc and estradiol led to increased production of reactive oxygen species.[5]

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Conflict of Interest Disclosures: Dr Cramer reported receipt of personal fees from Beasley Allen Law Firm for serving as a plaintiff's witness in talc litigation.

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To the Editor We disagree with the analysis and interpretation of the findings presented by Dr O'Brien and colleagues.[1] The increased risk of ovarian cancer in women with intact genital tracts exposed to powder (HR, 1.13) is actually greater than the estimated 10% increased incidence of ovarian cancer attributable to cumulative talc exposure with 10 000 or more applications previously reported in women with intact genital tracts.[2] The lack of association in women without an intact genital tract is consistent with their curtailed exposure. O'Brien and colleagues discounted the results because their statistical test for heterogeneity was not statistically significant. No statistical test is needed to know that women without an intact genital tract face a different risk of ovarian cancer than women whose genital tract is intact.

Furthermore, the study design likely underestimated the effect of powder on ovarian cancer risk. Meaningful lifetime exposure would typically start early in life but was assessed in these cohorts at a median age of 57 years, decades after first exposure and well into the hypothetical risk period for ovarian cancer. Restricting outcome assessment to women who survived to this age without having previously developed ovarian cancer introduces the potential for substantial selection bias, often called *depletion of susceptibles*.[3] Exposure was reported by recall, which may involve considerable misclassification and bias toward the null in this setting. Confounding variables were also assessed long after exposure was initiated, which can lead to control for mediators that attenuate causal effects. The widely varying definitions of ever exposed in the 4 included cohorts creates an ill-defined causal question, more misclassification, and potential bias toward the null.

To conclude that "there is no statistically significant association" based on an HR of 1.08 (95% CI, 0.99-1.17) is now recognized as poor practice in population and clinical research.[4,5] If the 95% CI had instead been 1.01 to 1.19, would the authors have had a completely different interpretation? Given that the authors reported a 13% increased risk of ovarian cancer among women with intact genital tracts who used powder, despite these methodological issues, this study should be taken as evidence of an effect.

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Conflict of Interest Disclosures: Dr Harlow reported publishing research and serving as a consultant on the topic of talc and ovarian cancer risk. No other disclosures were reported.

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In Reply As pointed out by Dr Cramer, the cohorts in our pooled analysis[1] assessed powder use with less detail compared with prior case-control studies. He is also correct that most participants were postmenopausal at enrollment, although ever use included premenopausal time and we considered menopausal status and hormone use as effect modifiers. We noted that genital powder exposure was likely misclassified for some individuals, especially with regard to frequency and duration, and we did not have data on changes in use over time, use during specific exposure windows, or use of different types of powder. This lack of detail may have biased our effect estimates toward the null.

Conversely, empirical evidence supports that recall bias is present in retrospective studies.[2,3] While true never users are unlikely to report daily use, some users may fail to report use and others may misreport frequency and duration of use or type of product used. If misclassification is differential by case status, it could influence effect estimates in case-control studies.

Considering the results of observational studies with different designs may help improve understanding of the

exposure-disease relationship. If cohort studies (pooled HR, 1.08)[1] are likely biased toward the null and case-control studies (meta-analysis OR, 1.35)[4] are likely biased away from the null, the true association may lie somewhere in the middle.

We completely agree with Dr Harlow and colleagues that our results, particularly the analyses limited to women with intact reproductive tracts, should not be discounted because of lack of statistical significance. For all estimates, we reported 95% CIs so readers could consider effect size and precision. The qualifier that there was no statistically significant association between ever genital powder use and ovarian cancer is a factual report of a test of the null hypothesis; we never equated the lack of statistical significance to evidence of no association.

We conducted subgroup analyses with an a priori hypothesis that intact reproductive tracts are required to be susceptible to the exposure. Therefore, even though we stated that findings from subgroup analyses should be interpreted as exploratory, we do not consider them all equally important and agree that the positive association among women with patent reproductive tracts (HR, 1.13; 95% CI, 1.01-1.26)[1] is consistent with the hypothesis that there is an association between genital powder use and ovarian cancer.

We agree with Harlow and colleagues that methodological limitations, such as nondifferential exposure misclassification, selection bias, and misspecified confounders, could bias the results, and we acknowledged many of these in our article. However, because of the rarity of ovarian cancer and the risk of recall bias in retrospective studies, we think that despite the limitations, the prospective cohorts included in the analysis offered important new data for addressing this question. While it is unlikely that other prospective cohorts with data on genital powder use will come along anytime soon, future analyses that quantify the underlying biases of observational studies could refine measures of true underlying associations.

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Ondansetron Use in Pregnancy and Congenital Malformations

To the Editor Dr Huybrechts and colleagues conducted a population-based cohort study of intravenous ondansetron use during pregnancy and congenital malformations and found no association.[1]

We wonder whether the difference in risk of cleft palate between oral[2] and intravenous[1] treatment could be explained by the shorter duration of treatment with intravenous therapy. Do the authors have additional information about the duration of intravenous treatment?

Also, did women in the intravenous ondansetron group receive oral ondansetron after intravenous treatment?

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Conflict of Interest Disclosures: None reported.

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In Reply Ms Saban and colleagues raise questions about treatment with intravenous ondansetron in our cohort study of congenital malformations. We reported an adjusted relative risk (RR) of oral clefts of 0.95 (95% CI, 0.63-1.43) for intravenous ondansetron[1] and 1.24 (95% CI, 1.03-1.48) for oral ondansetron in an earlier publication.[2] Although the point estimate is lower for intravenous ondansetron compared with oral ondansetron, the 95% CI was wide, with an upper limit similar to that for oral ondansetron. Although the increase in risk was statistically significant for oral ondansetron and was not for intravenous ondansetron, interpretation of risk estimates from epidemiological studies should focus on the magnitude of the observed increase in risk and the precision of the estimate and not on statistical significance alone.[3] Based on our analyses, given the width of the 95% CIs, there is insufficient evidence to conclude that the observed risks are different for intravenous vs oral ondansetron.

Although we captured administration of ondansetron injection using procedure codes, our data did not include information on the dose and duration of the intravenous treatment. The RR should be interpreted as that associated with intravenous ondansetron as it was administered in routine practice to pregnant patients in the United States during the study period.

Among the 23 877 women exposed to intravenous ondansetron in our original analyses, 11 772 (49%) also filled an outpatient prescription for oral ondansetron during the first tri-